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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/066,305	Applicant(s) GOLUB ET AL.	
	Examiner Karen A Canella	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3,4,7-9,12-14,16-20,23-29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 3, 4, 7-9, 12-14, 16-20, 23-29, 31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1, 3, 4, 7, 12-14, 16-18, 24--26, 31 and 32 have been amended. Claim 34 has been added. Claims 2, 5, 6, 15, 30, 33 and 34 have been canceled. Claims 1, 3, 4, 7-9, 12-14, 16-20, 23-29, 31 and 32 are pending and under consideration.

2. The text of title 35, U.S. code not cited in this action can be found in a previous action.

3. The rejection of claims 26-29 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in light of applicants amendments.

4. Claims 1, 3, 4, 7-9, 12-14, 16-20, 23-29, 31 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are rendered vague and indefinite in the recitation of M64347_at as the only means for identifying the claimed informative gene. M64347_at is a GenBank Accession number and therefore an object which is variable: the sequence represented by said accession number can be subjected to editing, and thus altered. Therefore, the claims are rendered indefinite as the claimed gene upon which the method claims depend is defined by an object which is variable.

Claims 12, 13, 24, 25, 28 and 29 are rejected for referring to Table 1 and Tables 2-6. The M.P.E.P. states that claims should stand alone and not rely on figures or Tables within the specification. Further, reference to the genes in Tables 1-6 is by GenBank Accession Numbers which are rejected as objects which are variable for the same reasons of record as M64347_at.

Claim 1 is vague and indefinite for failing to how the expression profile is correlated with a specific brain tumor type. Further the metes and bounds of two or more informative genes beyond the M64347 is also unclear.

Claims 8, 9, 19 and 20 lack active method steps, as the recitation of "utilizing" does not constitute a specific method step.

Recitation of "the sample" in claim 14 lacks antecedent basis within the claim.

Claim 23 is vague and indefinite in the recitation of "survival after treatment" without limitations as to how long said survival shall occur. Survival after treatment can encompass a length of time as small as an hour or a week, or a length of time such as 5 years, or 10 years.

Claim 26 is vague and indefinite in the recitation of "informative genes" . further it is unclear how the "magnitude" of the vote is to be determined because "depending on the expression level of the gene" does not accurately define the mathematical relationship between the gene expression and the magnitude of the vote; further, the relationship between the gene expression and class distinction is unclear. this lack of clarity stems from a lack of a definition for "class distinction" . Additionally, the claims are vague and indefinite because it is unclear if the level of gene expression used in the computation is a normalized or non-normalized level. Section (b) of claim 26 is vague and indefinite because "winning " would be a relative term. The specification nor claim provides a level at which the summation of votes is either "winning" or "loosing". Claim 26 is vague and indefinite in the recitation of "summing the votes" as referred to in the plural as it appears from section (a) that one informative gene is given a single weighted vote. It is unclear how a single weighted vote from one gene is to be subjected to "summing". The claim also fails to link by an active method step the summation of the votes to the determination of "the winning class" and further fails to link by an active method step said "winning class" with a treatment outcome class.

The metes and bound of claim 27 cannot be determined. Claim 27 fails to recite how a correlation is made between gene expression values and class distinction. Further it is unclear what constitutes "class distinction", therefore, the metes and bounds of the parameter ag cannot be determined. Claim 27 also recites "expression value in a first class and a second class". It is unclear what constitutes said first and second classes, therefore the metes and bounds of the parameter bg cannot be determined. It is unclear how a log10 gene expression value differs from the log10 gene expression level in the sample to be tested rendering the value of xg vague and indefinite. In addition, claim 27 recites "in the sample to be tested" in reference to the xg value. However, neither of claims 26 or 27 are drawn to a sample to be tested; they are drawn to a method of assigning a brain tumor sample to a treatment outcome class. Therefore, the reference to "gene expression value in the sample to be tested" is vague and indefinite as the sample would already have been tested for gene expression in order to determine the weighted vote for claim

26. Additionally, the claims are vague and indefinite because it is unclear if the level of gene expression used in the computation is a normalized or non-normalized level. It is unclear how a vote for the "first class" versus a vote for the "second class" in claim 27 effects the prediction of treatment outcome which is the method objective recited in claim 26.

Applicant argues that recitation of M64347_at is not vague and indefinite and would clearly define the claims such that infringement could be avoided. This has been considered but not found persuasive. If the sequence of M64347_at were altered at some time in the future, the metes and bounds of the instant claims would be unclear.
Applicant further argues that the M64347_at gene is not claimed. this argument is irrelevant. The instant method claims are reliant upon the precise identify of the disclosed genes.

With regard to claims 26 and 27, applicant argues that ag is clearly described as the correlation between a gene's expression value and a particular class, and that this value is a definite value in the assignment the relative importance of a gene for making a particular class distinction. This has been considered but not found persuasive. Applicants arguments regarding the ability of one of skill in the art to assign a value to ag that "is definite" do not satisfy the requirements of 112, second paragraph, which requires that the specification or the claim be defined in such a way as the metes and bounds are readily discerned. This is also applied to applicants arguments regarding the assignment of a value for bg and xg. It is not a question of a value that one of skill in the art can apply to these parameters, it is a question of the specification setting forth a definition which defines the values themselves.

5. The rejection of claims 1, 3, 4, 7-9, 12-14, 16-20 and 23-29 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons of record.

The claimed invention is drawn to a method of classifying a brain tumor or assigning a brain tumor to a treatment class, said methods comprising determining the expression profile of the M64347 gene. M64347 is identified in Table I as encoding the FGFR3. As was set forth in section 9 above, the claims are indefinite in that it is not clear what molecules are encompasses

within the description of M64347 or FGFR3, or what the definitions are for the parameters of claims 26 and 27.

The art teaches that FGFR3 is expressed in many areas of the brain and can be detected in a Northern blot as a 4.4 Kda transcript in addition to two higher molecular weight unspliced transcripts in the basal ganglia, caudate, putamen and thalamus from a normal individual (Thompson et al, Genomics, 1991, vol. 11, pp. 1133-1142, especially page 1136, under the heading "Expression of FGF3"). In situ hybridization to tissue sections indicates binding of a probe at high levels to the caudate, putamen, ventral mesencepehelon, the nucleus ruber, the substantia nigra, the frontal cortex , spinal cord gray matter, and Purkinje cells.

Abbass et al (Journal of Clinical Endocrinology and Metabolism, 1997, Vol. 82, pp. 1160-1166) teaches that all pituitary adenomas expressed FGFR3, isoform I, no pituitary tumor expressed only FGFR3, isoform K, and numerous tumors had a secretable form of FGFR3, in contrast with the normal pituitary gland which expressed both isoforms of FGFR3. Abbass et al teaches that there was no correlation between the expression profile of the FGFR and tumor type, size, or aggressiveness (abstract, second column, lines 16 and 17).

Wren et al (American Journal of Human Genetics, 2000, Vol. 67, pp. 345-356 identifies M64347 as a gene having allelic diversity within the human population (page 355, second column, line 11 under the heading "Electronic-Database Information", and page 346, under the listing for Human novel growth factor receptor). It is noted that another name for the protein encoded by M64347 is "Novel Growth Factor Receptor" as evidenced by Mack (U.S. 6,303,301) (Figure 10E, line 23). Wren et al teach that polymorphic repeats within transcribed sequences represent potentially large set of disease causing loci.

The specification mentions M64347 twice: once in Table 1 which has the heading "Markers Upregulated in High Risk, Downregulated in Low Risk", and once in Figure 3C, which appears to correlate the lowered expression of M64347 with a C1 group of "survivors". The scale at the bottom of figure 3C sets the dark blue color as between minus 2 and minus three standard deviations from the mean. The brief Description of the figures indicates that figure 3C lists fifty genes associated with treatment failure in Medulloblastoma. There are no teachings in the specification to correlate a value which is several standard deviations from the mean with a method of classifying a brain tumor or a method of predicting the efficacy of a brain tumor.

Firstly the specification does not teach whether the expression of the M64347 as shown in figure 3C was obtained from the brain tumor before treatment or after treatment. Secondly, it is unclear if the lowered expression of M64347 in the C1 and C0 survivor group is indicative or predictive of a treatment failure or a treatment success as the title of figure 3C seems to be "Markers of treatment Failure" but the heading in Table 1 indicates that M64347 is in the category of "markers downregulated with low risk". Thirdly, the specification does not teach define how the C1 or C0 groups were differentiated, nor does the specification actually teach what constitutes a treatment failure or success, in terms of disease free survival or length of survival.

There is no guidance for a specific polynucleotide probe and hybridization conditions to be used in the determination of an expression profile for the classification of a brain tumor, or the method of predicting the efficacy of treatment. It is noted that Abbass et al teach multiple isoforms for the FGFR3 gene as well as the presence of unspliced mRNA in brain tumors. Wren et al teach that the M64347 gene actual contains polymorphisms that potential can render it disease causing. It is obvious that an oligomer derived from M64347 could hybridize to any number of the polymorphic gene products or splice variants or alleles of M64347 as a function of its particular sequence. The specification provides no teachings as to the exact nature of the probe used for the expression profile, thus it cannot be construed from the specification which polymorphic variants, splice variants or alleles are integral to the claimed invention. Given these teachings and the lack of teaching in the specification regarding a specific probe and hybridization conditions for the determination of an expression profile of M64347, one of skill in the art would be subject to undue experimentation as the specific gene product referred to in the claims is undefined and further as the specification does not address the use of the M64347 gene for the classification of a brain tumor as medulloblastoma or glioblastoma.

In the case of claims 26-29, as the specification does not define the parameters needed to calculate weighted vote for M64347, therefore the specification is not enabling for said claims.

Given the lack of specific teachings in the specification regarding the expression of the M64347_at gene in the classification of brain tumor sub-types and for predicting the efficacy of treatment, and the state of the art regarding the polymorphic nature of the M64347 gene and the isoforms of FGFR3 expressed therefrom, and the lack of specific definitions for calculating the weighted vote of claims 26 and 27, and the lack of teachings in how to apply said weighted voted

to the prediction of treatment outcome as recited in the pre-amble of claim 26, one of skill in the art would be subject to undue experimentation in order to practice the claimed methods.

Applicant argues that the specification is fully enabling for the determination of the expression profile for M64347_at, and that it is the detection of the gene expression products rather that the gene itself that leads to the creation of the expression profile. This has been considered but not found persuasive. One of skill in the art could certainly measure the gene expression products of M64347, however, the specification is not enabling for the correlation of the obtained expression profile with the classification of the brain tumor type and the prediction of therapeutic efficacy for the reason set forth above.

Applicants argue that the allelic diversity of M64347 has no bearing on the instant methods as one of skill in the art would clearly be aware of allelic variation and employ detection methods that would buffer the effects of polymorphic variation. This has been considered but not found persuasive. Without specific guidance from the specification, it is unknown if the correlation between the expression of M64347_at and medulloblastomas and glioblastomas is dependent upon a specific mutation or polymorphism. One of skill in the art would be subject to undue experimentation by using detection methods which would exclude the region of the expressed sequences which was actually indicative of meduloblastoma or glioblastoma, or which was crucial for the prediction of treatment outcome. Applicants arguments regarding the teachings of Golub et al for methods of determining class and subclass as set forth in U.S. application No. 09/544,627 are unpersuasive. In the event the instant application wee to issue before the '627 application, the public would not be apprised of the teachings of Golub et al, and therefore would not be able to use the instant invention.

Applicant argues that Figure 3C represents a tabular distribution of fifty genes most associated with favorable or unfavorable treatment outcome. This is not persuasive. Firstly the specification does not teach whether the expression of the M64347 as shown in figure 3C was obtained from the brain tumor before treatment or after treatment. Secondly, it is unclear if the lowered expression of M64347 in the C1 and C0 survivor group is indicative or predictive of a treatment failure or a treatment success as the title of figure 3C seems to be "Markers of treatment Failure" but the heading in Table 1 indicates that M64347 is in the category of "markers downregulated with low risk". Thirdly, the specification does not teach define how the

C1 or C0 groups were differentiated, nor does the specification actually teach what constitutes a treatment failure or success, in terms of disease free survival or length of survival.

6. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Au-Young et al (U.S. 6,500,938, cited in a previous Office action) in view of Abbass et al (Journal of Clinical Endocrinology and Metabolism, 1997, Vol. 82, pp. 1160-1166, cited in a previous Office action).

Claim 31 is drawn to a method for evaluating drug candidates for their effectiveness in treating brain tumors comprising obtaining a sample of cells derived for a brain tumor and correlating the expression profile of M64347 with the effectiveness of the drug candidate in the treatment of brain tumors. Claim 32 is drawn to a method for monitoring the efficacy of a brain tumor treatment comprising determining gene expression profiles at multiple times during treatment of a patient by measuring the levels of polynucleotide gene expression products from tow or more informative genes from one or more cells derived from brain tumor, wherein one of said informative genes is M64347_at; and determining the treatment outcome at each time based on the gene expression profile.

Au-Young et al teach a method for monitoring the progression of a disease or the efficacy of a treatment comprising detecting an expression profile by means of a microarray (column 11, line 15 to column 12, line 67). As Au-Young et al specifies the monitoring of diseases, it is inherent that samples are obtained from patients being treated at various time points. Further, the detection of cancer as disclosed by Au-Young appears to be identical to the "prediction of tumorigenesis" as claimed. Au-Young et al teach cancers of the brain as a specific embodiment (column 11, lines 11-12). Au-Young et al teach that the methods can be used for monitoring the progress of disease and efficacy of treatment and can also be used to generate expression profiles of therapeutic agents and that this can allow for the rapid screening of large numbers of drug candidates to find ones that have the same expression profile as known therapeutic agents (column 11, lines 50-59 and column 12, lines 42-58). Au-young et al specifically teach "This invention allows researchers to develop sophisticated profiles of the effects of the currently available therapeutic drugs. tissues or cells treated with these drugs can be analyzed using this invention, and compared to untreated samples of the same tissues or cells. In this way, and

expression profile of known therapeutic agents will be developed. Knowing he identity of sequences that are differentially regulated in the presence or absence of a drug will allow researchers to elucidate the molecular mechanisms of action of that drug. also, researchers can use the invention to rapidly screen large numbers of candidate drugs, looking for ones that have an expression profile similar to those of known therapeutic drugs , with the expectation that molecules with the same expression profile will likely have the same therapeutic effects" (column 12, lines 42-57). Au-Young et al do not teach the expression profile of M64347 or the FGFR3 encoded thereby.

Abbass et al teach that the expression of the mRNA encoding the secreted form of FGFR3, which would be expressed from the M64347_at gene, is correlated with pituitary adenomas.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use probes derived from the M64347_at gene in the microarray as taught by Au-Young to obtain the expression profile of the secretable form of the FGFR3 in the method for evaluating drug candidates for their effectiveness in treating pituitary adenomas, and monitoring the efficacy of treatment of pituitary adenoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Abbass et al on the unique expression of the secretable form of FGFR3 mRNA in pituitary adenomas versus the lack of expression of the secretable form of this receptor in normal pituitary. One of skill in the art would be motivated to use polynucleotide encoding said secretable receptor in a method for evaluating drug candidates, as lack of expression of said polynucleotide would indicate that the samples of cells were exhibiting gene expression consistent with a normal pituitary gland and the attainment of a normal phenotype, and increase or no change in the expression of said polynucleotide would indicate that the drug did not have efficacy as the sample of cells was expressing a polynucleotide indicative of tumorigenic cells. thus, monitoring the decreasing in expression of M64347 over time would be indicative of an efficacious treatment . Insertion of probes and oligonucleotides derived from M64347_at into the array of Au-Young et al satisfies the specific embodiments of claims drawn to "two or more informative genes"

7. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (U.S. 6,218,122, cited in a previous Office action) in view of Abbass et al (Journal of Clinical Endocrinology and Metabolism, 1997, Vol. 82, pp. 1160-1166). The specific embodiments of the claims are recited above.

Friend et al teach a method for detecting changes in a biological state of a subject which are correlated to one or more disease states and methods for monitoring the efficacies of a therapy or therapies upon a subject, said methods comprising the determination of an expression profile from said cells in said patient (column 3, lines 7-49, column 9, lines 1-19). Friend et al teach glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, oligodendroglioma, meningioma and neuroblastoma (column 8) and medullary carcinoma (column 7) as diseases encompassed by the invention, thus fulfilling the specific embodiment of brain cancer (Table I). As Friend et al teach the detection of changes in a biological state, therefore the specific embodiment of claims 32 with respect to obtaining cells at various time points obtained from a patients are inherent within the method, as the act of monitoring encompasses sampling over time. Friend et al do not teach the expression profile of M64347 or the FGFR3 encoded thereby.

Abbass et al teach that the expression of the mRNA encoding the secreted form of FGFR3 which would be expressed from the M64347_at gene is correlated with pituitary adenomas

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to use probes derived from the M64347_at gene in the microarray as taught by Friend et al to obtain the expression profile of the secretable form of the FGFR3 in the method for evaluating drug candidates for their effectiveness in treating pituitary adenomas, and monitoring the efficacy of treatment of pituitary adenoma. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Abbass et al on the unique expression of the secretable form of FGFR3 mRNA in pituitary adenomas versus the lack of expression of the secretable form of this receptor in normal pituitary. One of skill in the art would be motivated to use polynucleotide encoding said secretable receptor in a method for evaluating drug candidates, as lack of expression of said polynucleotide would indicate that the samples of cells were exhibiting gene expression

consistent with a normal pituitary gland and the attainment of a normal phenotype, and increase or no change in the expression of said polynucleotide would indicate that the drug did not have efficacy as the sample of cells was expressing a polynucleotide indicative of tumorigenic cells. Thus, monitoring the decreasing in expression of M64347 over time would be indicative of an efficacious treatment . Insertion of probes and oligonucleotides derived from M64347_at into the array of Friend et al satisfies the specific embodiments of claims drawn to "two or more informative genes"

8. All other rejections and objections as set forth in Paper no. 9 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
December 21, 2003